Acute and Chronic Asthma

Treatment with Theophylline in Hydro-Alcoholic Solution: Clinical Evaluation and Pulmonary Function Studies

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• **A flavored solution containing 80 mg. of theophylline and 3 cc. of ethyl alcohol per 15 cc. was given orally to 31 patients with acute asthma to terminate the attack. Thirty patients with moderate to severe chronic asthma were alternated for three or four weeks on daily multiple doses of either the theophylline solution or a placebo.**

In the acute cases three-second Vital Capacity increased by 33.8 per cent and Maximal Breathing Capacity by 30.2 per cent in one hour after taking 60 cc. to 75 cc. of the theophylline solution. When placebos were given, both measures of lung function declined during the first half hour.

Seventy-one and a half per cent of patients with acute cases felt moderate to complete relief of symptoms. In persons with chronic asthma the regular use of the theophylline solution did not change the frequency of asthma in most cases, but it decreased the severity in 59 per cent of cases. The values for three-second Vital Capacity and Maximal Breathing Capacity rose only a little.

Gastric irritation was noted in one-third of the chronic cases and one-fourth of the acute cases. This could be reduced by appropriate measures.

THEOPHYLLINE IS OF GREAT VALUE in relaxing the bronchospasm of asthma. Waxler and Schack[5] showed that in acute cases the effective blood level was 6 micrograms or more per milliliter. In order to obtain this level rapidly, they noted, it was necessary to give 250 mg. of aminophylline intravenously. When aminophylline was taken by mouth in the usual tablet form, the theophylline level in the blood a half hour after ingestion was only 2 mcg. per milliliter.

To avoid the difficulty of intravenous administration, advantage may be taken of the observation by Schluger, McGinn and Hennessy[3] that theophylline in an alcohol-water solution is rapidly absorbed from the intestinal tract.* The preparation they studied, Elixophyllin, contains in each 15 cc. (one tablespoon) 80 mg. of theophylline, which is equivalent to 100 mg. of aminophylline. In addition, each 15 cc. contains 3 cc. of ethyl alcohol, and flavoring agents.

Seventy-five cubic centimeters of Elixophyllin (400 mg. theophylline) taken by mouth was followed by mean theophylline blood levels of 8.0 mcg. per milliliter in 15 minutes, 10.3 mcg. per milliliter in 30 minutes and 11.0 mcg. per milliliter in one hour. In contrast, ingestion of 500 mg. of aminophylline in tablet form resulted in theophylline levels of 1.1, 3.8, and 7.2 mcg. per milliliter in 15, 30 and 60 minutes, respectively. Increasing the dose of aminophylline tablets usually caused gastric distress.

Because of the potential usefulness of a rapidly acting bronchodilator that can be taken by mouth, a study of the use of Elixophyllin in two groups of patients, one with acute asthma and the other with chronic asthma, was carried out.

ACUTE ASTHMA

Materials and Methods

Thirty-five patients, 13 to 74 years of age, who came either to the Los Angeles County General Hospital or to the author's office cooperated in this part of the study. Patients who were in severe status asthmaticus with dehydration, or who had obvious signs of infection, or who had been given aminophylline within two hours were excluded. In the group selected there were 15 males and 20 females, all of whom had had moderately severe to severe asthma for at least two years. The majority were between 40 and 60 years of age.

As soon as the patient had been examined and found acceptable for the study, tracings were made of the 3-second vital capacity (timed vital capacity or T.V.C.) and the 15-second maximal breathing capacity (M.B.C.), using either a Stead-Wells or Collins 13-liter recording respirometer. Each patient was then given either Elixophyllin or a placebo. Men were given 75 cc.; women and older children received 60 cc. The placebo used was flavored to resemble the base of Elixophyllin, and contained 3.5 mg. of quinine hydrochloride per 15 cc., to equal the bitter taste of theophylline. The amount of quinine was only a small fraction of the least medicinal dose. The placebo in this part of the study also contained 20 per cent ethyl alcohol.

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*The preparation they studied was Elixophyllin, a product of Sherman Laboratories, whose support made this study possible.

At the beginning of the study alternate patients were given Elixophyllin and placebos. If the patient's condition did not improve in a half hour after the placebo, he was given an equal amount of Elixophyllin. As the first ten controls showed no improvement or got rapidly worse in the half hour after the placebo was given, it did not seem worth while continuing the placebo test in acute cases. The alcohol content and the factor of suggestion appeared to have no effect.

Pulmonary function readings were taken 15 minutes, 30 minutes, one hour, two hours (and in some cases three to six hours) after the single dose of Elixophyllin and at 15 and 30 minutes after the placebo. Several days later, when the patient had returned to his usual condition, another set of readings was taken.

The actual readings for T.V.C. and M.B.C. were converted to "per cent of expected normal" for each patient, using the formulae of West[6] and Motley.[2]

Results

Relief was judged as *complete* if symptoms had cleared in one hour, *pronounced* if no further treatment was needed but some wheezing persisted, *moderate* if air hunger was relieved but epinephrine was needed for residual wheeze and cough, and *slight* if the patient felt a little better and had a measurable increase in lung function.

Results in terms of degree of relief are shown in Table 1. Complete relief was the exception. About one third of the patients were relieved to the extent that no other medication was needed for the moment, and another one third required only a small amount of supplemental medication. The remaining third of the group received little or no benefit. The patients given placebo showed no improvement in symptoms or measurable lung function.

The average values for T.V.C. and M.B.C. at intervals of 15, 30, 60 and 120 minutes after Elixophyllin are plotted in Chart 1. The initial values of each function were low for the group as a whole—only 37.7 per cent and 29.5 per cent, respectively, of expected normal. As a matter of interest the curve of blood theophylline after 75 cc. of Elixophyllin, as determined by Schluger, McGinn and Hennessy,[2] was included in the graph on a separate scale. The parallel between the theophylline level and the change in average lung function was striking. This depression of lung function was consistent with the severe symptoms present. Table 2 gives the values from which Chart 1 was drawn.

On the average, improvement was noticeable within 15 minutes and reached its peak in around one hour. Subsequently, the average improvement declined, although not in all cases were readings lower at two hours than at one hour.

TABLE 1.—*Relief of Acute Asthma in 35 Patients Treated with Elixophyllin and Placebo*

Degree of Relief*	Elixophyllin		Placebo	
	No. Cases	Per Cent	No. Cases	Per Cent
Complete	2	5.7	....	....
Pronounced	11	31.5	....	....
Moderate	12	34.3	....	....
Slight	8	22.8	....	....
None	2	5.7	10	100†

*Criteria given in text.
†Only ten patients given placebos.

TABLE 2.—*Timed Vital Capacity and Maximal Breathing Capacity (Average Values) as Per Cent of Predicted Normal in 35 Patients with Acute Asthma Treated with Elixophyllin*

Time After Drug Given	Per Cent of Predicted Normal	
	3-Sec. T.V.C.	M.B.C.
0	37.7	29.5
15 min.	41.3	32.0
30 min.	47.0	35.8
1 hr.	50.4	38.4
2 hr.	47.1	35.5
After recovery	64.4	55.5

The values for T.V.C. and M.B.C. taken after recovery from the acute attack show that there is constantly present in these cases a large measure of impairment in lung function.

Although not apparent from the average figures, ten patients (29 per cent) showed slightly poorer function at 15 minutes after Elixophyllin than before taking it, and five (14 per cent) were still slightly below initial reading at 30 minutes. All these patients had responded by the end of an hour. Differences in rate of absorption may account for the slow response. But it could also be explained by assuming that factors other than bronchospasm are causing part of the obstruction to air flow.

The per cent of change of the T.V.C. and M.B.C. after Elixophyllin is given in Table 3. These values (for T.V.C.) compare well with the improvement after Elixophyllin noted by Spielman.[4] In his series of 20 patients with acute asthma, vital capacity increased 39 per cent.

The most prominent complaint about Elixophyllin in the acute cases was burning in the stomach with or without some nausea. Nine, or about twenty-five per cent, of the patients mentioned this. Only one patient actually vomited, and was excluded from this series. Feeling light-headed or dizzy was a frequent but minor complaint, made only by women patients. Two women went through a weeping spell shortly after taking 60 cc. of Elixophyllin, but soon calmed down.

The data presented in this section suggest that on the average Elixophyllin relieves bronchospasm and increases pulmonary function in patients who are having acute exacerbations of asthma. After a single

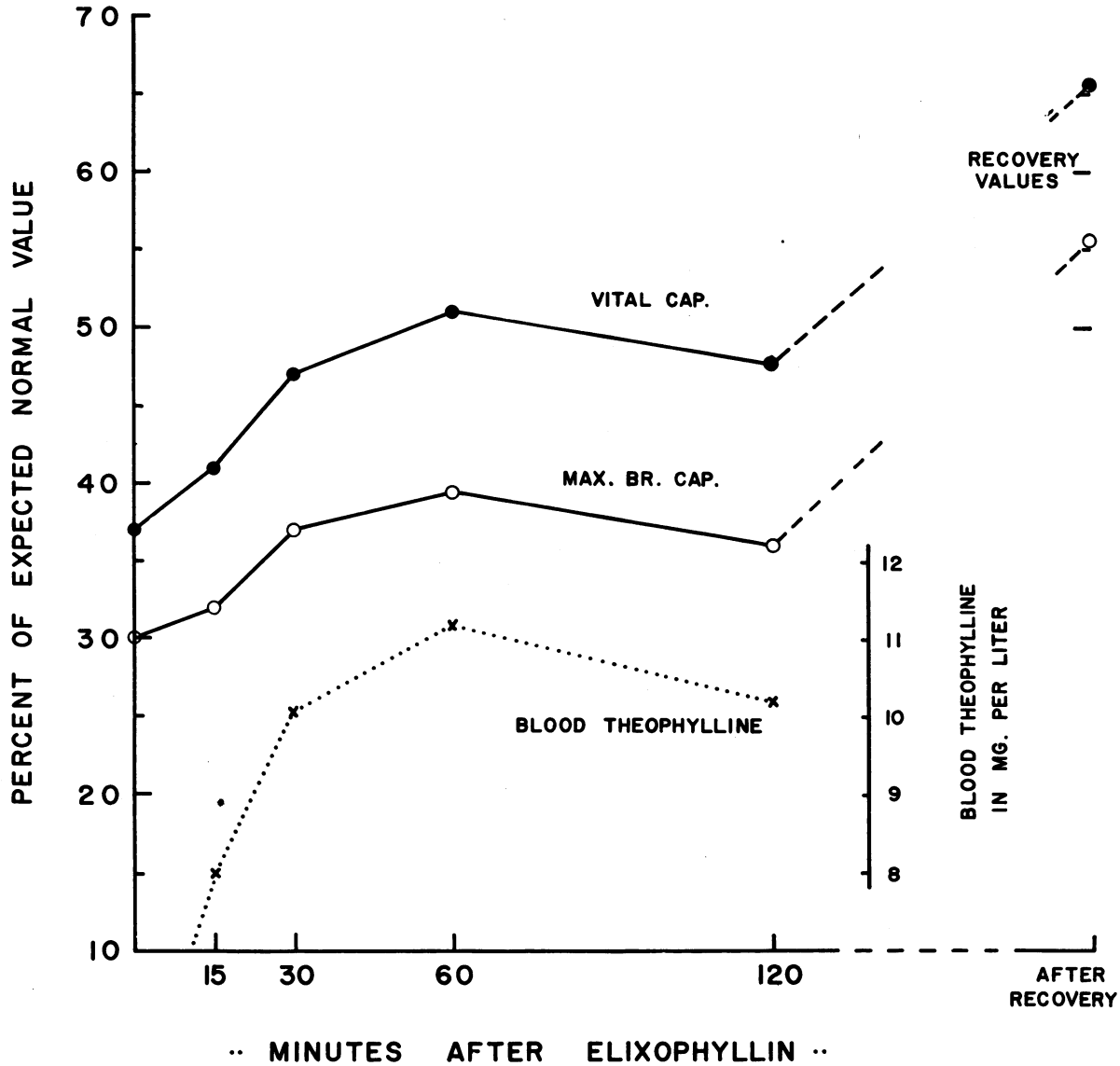

Chart 1.—Effect of Elixophyllin on 3-second Vital Capacity and Maximal Breathing Capacity of patients who received the drug during acute phase of bronchial asthma. The dotted line at bottom of chart shows the theophylline content in the blood after administration of 75 cc. of Elixophyllin (400 mg. theophylline), as determined by Schluger, McGinn and Hennessy.[3]

dose of 75 cc. (400 mg. theophylline) improvement was noted on the average within 15 minutes, continued up to one hour, and then tended to decline.

Nearly all the patients studied had some decrease in lung function even between attacks. Since single doses of Elixophyllin usually did not raise lung function to the resting level and tended to lose their effectiveness after two hours, the dose may be repeated at intervals to maintain maximum benefit. As individuals vary widely, the need for extra Elixophyllin should be judged by the patient's response. Allowance should also be made for the fact that about one third of patients may not respond in the first 15 minutes after taking Elixophyllin.

TABLE 3.—*Change from Initial Values of Timed Vital Capacity and Maximal Breathing Capacity in Cases of Acute Asthma*

Treatment	Timed Vital Capacity — Per Cent Change	Maximal Breathing Capacity — Per Cent Change
After Placebo, 10 cases.....	15 min.— 0.5	— 4.5
	30 min.—10.1	— 8.5
After Elixophyllin, 35 cases.....	15 min.+ 9.6	+ 8.5
	30 min.+24.6	+21.4
	1 hr.+33.8	+30.2
	2 hr.+25.0	+20.4

Materials and Methods

Thirty-six patients with chronic asthma were selected from clinic and private patients to take Elixophyllin and a placebo for three to four weeks each. Six patients had to be dropped from the study because of side effects from Elixophyllin. Of the 30 remaining patients, 14 were males and 16 females. The youngest was 4 years of age, the oldest 74, and the median for the group was 50 years. The average duration of asthma was seven years, although many of the patients had had the disease their life long. Seven of the thirty patients were classed as having moderate asthma, as they were prevented from working and used daily medication. Twenty-three had severe asthma and required frequent emergency treatment.

The dose of both Elixophyllin and placebo was 60 cc. (4 tablespoons) four times a day for adult males, and 45 cc. (3 tablespoons) for women and adolescents—320 mg. and 240 mg. of theophylline, respectively. These amounts were often decreased slightly by the patients themselves, depending on the amount of relief experienced.

Each patient kept a daily record of asthmatic attacks, coughing spells, supplemental medication and an estimate of over-all improvement in symptoms or lack of improvement. (After a short period of trial, patients are able to keep records that are more reliable than memory.[1]) These data were checked each week, and the number of attacks of asthma and/or coughing per week was designated the Symptom Index. The degree of relief was rated from none (0) to complete (4). Thus complete control of asthma for a week would make the Symptom Index zero, and conversely the degree of relief would be 4.0. The more the symptoms the greater the Symptom Index, and less than complete relief would result in some value between 0 and 4.0.

During the control period, and once a week during the treatment period each patient was checked for T.V.C. and M.B.C. The measurements were taken at mid-morning, after the patient had been sitting quietly for a half hour. Readings were taken with the patient standing. The values obtained were converted to per cent of expected normal in each case.

Results

As shown in Table 4, lung function improved modestly in the group as a whole during the time Elixophyllin was being taken regularly. Before treatment the average value for T.V.C. was 49.7 per cent of normal; during the month of Elixophyllin administration it rose to 58.5, an increase of about 15 per cent. The placebo caused no change on the average from the initial value.

TABLE 4.—*Average Values Before and During Treatment with Elixophyllin and Placebo Among Thirty Patients with Chronic Asthma.*

	Initial Value	Under Elixophyllin Therapy	With Placebo
Timed Vital Capacity (Per cent of normal)	49.7	58.5	49.9
Maximum Breathing Capacity (Per cent of normal)	35.6	42.9	33.5
Symptom Index (Weekly Average)	23.9	19.5	22.7
Degree of Relief* (Weekly Average)	....	2.38	1.08

*No relief 0; complete relief 4.0.

The other function measured, M.B.C., rose from 35.6 per cent to 42.9 per cent of predicted normal during the use of Elixophyllin, an increase of 20 per cent. Again the placebo produced no change on the average from the initial readings.

The Symptom Index, which is primarily a measure of the frequency of asthmatic attacks, showed only a slight decrease during Elixophyllin therapy. The difference in the Degree of Relief Index, however, was large; it was twice as much during Elixophyllin as during placebo administration. This was borne out by typical comments from patients, such as: "much lighter attacks"; "can bring up mucus"; "easier to stop attacks," etc. This would indicate that Elixophyllin used on a regular schedule decreased the severity of asthma in this group, without altering the basic pattern of the attacks.

Although only one of the 30 patients was completely relieved of asthma by Elixophyllin, 18 noted substantial benefit. The placebo was associated with slight to moderate relief in two patients, a rather lower incidence of placebo effect than was expected, which may indicate that in this type of severe intrinsic asthma psychologic factors are less important than organic factors.

The outstanding complaint regarding Elixophyllin was nausea, and some patients noted gastric irritation. These phenomena were most pronounced when the solution was taken on an empty stomach, and they varied with the amount taken. Six adult patients originally scheduled for this study were unable to continue; five because of nausea with or without cramps and diarrhea, or nausea and increase in asthma, and one because of increase in bronchospasm with each dose of Elixophyllin.

The side effects noted are listed in Table 5. During the full initial dose of Elixophyllin, a total of ten patients complained of some degree of gastric disturbance, but they were willing to continue because of the effect on their asthma. Gastric distress became less of a problem if Elixophyllin was taken when some food was present in the stomach, and as the dose was decreased after the test period.

An itching erythematous rash on the neck, back, chest and upper arms appeared in one patient during the third week of Elixophyllin therapy. It cleared when Elixophyllin was replaced by the placebo, and reappeared when the drug was tried again.

The placebo was associated with nausea in one patient and with an increase in asthma in another.

DISCUSSION

The study presented here indicates that a hydroalcoholic solution of theophylline when taken by mouth in adequate doses brings about an increase in pulmonary function in asthma. In acute attacks the effect is usually noticeable in 15 minutes and increases for an hour. Response is not this rapid in all cases, indicating that there may be different rates of absorption, or that factors other than bronchospasm are important. Patients who do respond well to Elixophyllin (37 per cent of the patients with acute cases in the present series) may be spared the inconvenience of intravenous aminophylline in many of their attacks, and can assume more responsibility for their own treatment. Those who do not respond readily will require intravenous aminophylline or hospital treatment.

Spielman[4] in reporting on 20 cases of acute asthma found that all of them noted good to excellent relief of symptoms after 75 cc. of Elixophyllin. In the present series of 35 cases of acute asthma, ten obtained practically no relief. The difference may be explained by the fact that the patients in Spielman's study had less initial depression of lung function and were better able to respond to the bronchodilator.

In chronic asthma the routine use of Elixophyllin decreases the severity of bronchospasm but does not alter the basic pattern of the disease except in a very few cases. In this respect it has the same effect as other forms of theophylline. Gastric distress with continuous use was complained of by a third of the patients, but this tended to disappear when the dose was reduced or if taken along with some food.

TABLE 5.—*Side Effects Complained of by Thirty Asthmatic Patients Receiving Elixophyllin and Placebos*

Side Effect	Elixophyllin No. of Cases	Placebo No. of Cases
Nausea		
Mild	3	0
Moderate	4	1
Severe	2	0
Vomiting	2	0
Cramps	1	0
Diarrhea	1	0
Insomnia	1	0
Headache	1	0
Rash	1	0
Asthma	0	1

Elixophyllin appears from this study to be a useful preparation for the control of bronchospasm in asthma. As with other methods of treatment, its use must be adjusted to the individual patient's needs, as dictated by experienced and clinical judgment.

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